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ON

# PYREXIN OR PYROGEN

AS A

# THERAPEUTIC AGENT.

BY

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# ON PYREXIN OR PYROGEN AS A THERAPEUTIC AGENT.

In studying the experimental evidence bearing on the germ theories of disease, I was greatly struck by a remark made by Dr. Burdon Sanderson in the *British Medical Journal* of 13th February, 1875. It was as follows: "Let me draw your attention to the remarkable fact that no therapeutical agent, no synthetical product of the laboratory, no poison, no drug is known which possesses the property of producing fever. The only liquids which have this endowment are liquids which either contain Bacteria, or have a marked proneness to their production." This last clause is qualified by the statements elsewhere, and from other sources, that the fever-producing agent is a chemical non-living substance formed by living Bacteria, but acting independently of any further influence from them, and formed not only by Bacteria but also by living pus-corpuscles, or the living blood- or tissue-protoplasm from which these corpuscles spring. This substance when produced by Bacteria is the *Sepsin* of Panum and others, but in view of its origin also from pus, and of its fever-producing power, Dr. B. Sanderson names it *Pyrogen*. If, however, it is to be also used therapeutically, I suggest the more neutral name of *Pyrexin*. I cannot admit without qualification the statement that no drug or poison can produce fever, for undoubtedly *Aconite*, *Belladonna*, *Arsenic*, *Quinine*, *Baptisia*, *Gelseminum*, and a host of other drugs do produce more or less of the febrile state among other effects. But they produce it only after repeated doses and contingently on the predisposition of the subject of experiment, and thus uncertainly as regards any individual case or dose; or they produce it as a part of a variety of complex local and general morbid states, of which it may be a secondary phenomenon. It is therefore practically true

that no other known substance induces idiopathic pyrexia certainly, directly, and at will after a given dose. This directness and certainty of action ought to make it a remedy of the highest value if it ever can be used therapeutically; and if the law of similars is applicable here as it is in so many other instances, we ought to find it curative in certain states of pyrexia and certain blood-disorders to which its action corresponds pathologically. In order to put this suggestion to the test practically, let us first shortly sum up the symptoms and pathological changes caused by *Sepsin* or *Pyrogen* freed from all bacterial, self-reproductive, or transmissible cause of disease. In a series of experiments by Dr. B. Sanderson on dogs after a non-fatal dose of *Pyrogen* (*i.e.* $1\frac{1}{4}$ cubic centimétre of the aqueous solution per kilogram of body weight, or $\frac{1}{2}$ grain of the solid extract for an ordinary sized dog), the animal shivers and begins to move about restlessly; the temperature rises from 2° to 3° C., the maximum being reached at the end of the third hour. There is great muscular debility; thirst and vomiting come on, followed by feculent and thin mucous, and finally sanguinolent, diarrhœa and tenesmus. These symptoms begin to subside in four or five hours, and the animal recovers its normal appetite and liveliness with wonderful rapidity. I mention this fact as proving that the septic poison has not the slightest tendency to multiply in the organism, and secondly, as rendering it extremely probable that when death occurs it is determined not so much by alvine disorders, which are so prominent, as by the loss of power of the voluntary muscles and of the heart.* Another proof that death when it occurs is from failure of the circulation is, that in non-fatal cases with well-marked gastro-enteric symptoms, the temperature rises gradually during the first four hours, and as gradually subsides; whereas in fatal cases it rises rapidly to 104° F., and then declines rapidly to below the normal before death, thus indicating failure of the heart. In fatal cases from larger doses, the above symptoms increase to intestinal hæmorrhage, purging, collapse, and death. *Post mortem.*—

* *Brit. Med. Journ.*, ii, 1877, p. 913.

There is found extravasation of blood in patches underneath the endocardium of the left ventricle, sometimes on the papillary muscles, sometimes on or in the neighbourhood of the valvular curtains. Similar though less marked appearances are seen in the right ventricle. There are similar points of ecchymosis on the pleura and pericardium. The spleen is enlarged and full of blood. The mucous membrane of the stomach and small intestine is intensely injected with detachment of the epithelium, and exudation of sanguinolent fluid distends the lumen of the gut. These appearances indicate a general tendency to congestion and capillary hæmorrhage, as well as locally, congestion and capillary stasis of the gastro-intestinal mucous membrane, with shedding of the epithelium, as the nature of the disorder. The state of the blood plays a great part in the morbid process; it is darker in hue, and the corpuscles arrange themselves in clumps instead of rolls; many of the blood-corpuscles are partially dissolved in the *liquor sanguinis*, communicating to it a red colour: a large quantity of the hæmoglobin is lost by evacuation of the bowels, and conversion into bilirubin; the partial disintegration of the white corpuscles, by liberating the fibrino-plastic ferment, is supposed to be one cause of the capillary stasis.

The symptomatic and pathological effects are substantially the same in man, and, indeed, the analogy between the symptoms and morbid appearance and state of the blood in septicæmia after wounds and the experimental poisoning with *Sepsin* is very close.

Now, granting that the powerful agent producing these remarkable effects may be expected to act therapeutically as an alterative in morbid states which present the pathological *simile* to them, what are these morbid states, and how are they to be recognised in the complex phenomena of fever in the human subject? To answer this we must enquire what is the cardinal point in the proximate cause of pyrexia with which we have to deal in employing a directly acting remedy? To this question—at least as regards the chief phenomenon which determines the name pyrexia, viz. the increased heat—the critical review of the

experiments of Senator, Leyden, and others by B. Sanderson,* gives a reply.

The temperature of the body being dependent on the production and discharge of heat, of which the former is a function of living protoplasm, the latter a function of the organs of circulation, respiration, and secretion, the question arises whether pyrexial increase of temperature depends upon the former or the latter. To this Dr. B. Sanderson thus replies (p. 45):—"Two possibilities are open to us. One is, that fever originates in disorder of the nervous centres, that by means of the influence of the nervous system on the systemic functions, the liberation of heat at the surface of the body is controlled or restrained, so that 'by retention' the temperature rises, and, finally, that the increased temperature so produced acts on the living substance of the body, so as to disorder its nutrition. The other alternative is that fever originates in the living tissues, that it is from first to last a disorder of the protoplasm, and that all the systemic disturbances are secondary. The facts and considerations we have had before us are, I think, sufficient to justify the definitive rejection of the first hypothesis in all its forms; for, on the one hand, we have seen that no disorder of the systemic functions, or of the nervous centres which preside over them, is capable of inducing a state which can be identified with febrile pyrexia; and, on the other, that it is possible for such a state to originate and persist in the organism after the influence of the central nervous system has been withdrawn from the tissues by the severance of the spinal cord. We are, therefore, at liberty to adopt the tissue-origin of fever as the basis on which we hope eventually to construct an explanation of the process." It is elsewhere concluded that it is in the protoplasm of the blood and the muscles that take place those changes of activity and disintegration on which depend the changes of temperature, and no doubt the other essential phenomena which characterise fever.

What, therefore, on these data, are we to expect from an agent which shall act directly as curative of the pyrexial

* See *Blue Book*, 1876, No. 1, Appendix.

state? Not certainly any palpable disturbance of the nervous system which can in health lower temperature by promoting heat discharge as is expected from large doses of *Quinine,* or from the merely physical action of cold baths; nor a general support of the vital powers till the specific disease runs its course, as is expected from alcohol, &c. But, on the contrary, a simple modification of the exalted and perverted protoplasmic action in which the proximate cause of pyrexia consists, which shall be of such a nature as to bring it back to health. Let us assume (without any attempt to prove it, but merely to give an intelligible illustration in explanation) the hypothesis of Beale, that the essence of inflammation and fever consists in a degeneration in the scale of biological development of the bioplasts of the blood and tissues, which involves the production of a more rapidly growing and disintegrating kind of protoplasm; our most complete and perfect conception of a direct remedy would be that of an agent which would act as a specific stimulus to the affected protoplasm, and bring back its germinal development up to the normal plane. This has long been my view of the action of *Aconite* in inflammatory fever, or, at least, that it acted directly on the pyrexically affected protoplasm, and not on the vaso-motor nerves or centres of the heart, or of the spinal marrow; for reiterated experience has shown that it acts in far too small a dose to exert any directly depressant effect on the heart or its nerves, or, indeed, any perceptible effect on them at all. Now, the living matter or protoplasm is capable of an almost infinite variety of kinds of morbid action according to the predisposing and exciting causes acting on it, and hence pyrexia may vary indefinitely in its character, even independently of the addition of the local lesion proper to the concrete specific fevers; so no directly curative remedy can be applicable to more than a few forms or even to only one, *e.g. Aconite* suits inflammatory fevers, and *Quinine* malarious intermittents, while they would be powerless if interchanged. To what form then should we expect *Pyrexin* or *Pyrogen* to be applicable? The true clue to this is given, I think, by the state of the blood, for

that is the most marked and important of the signs of septicæmia; the local congestions and extravasations not being so constant or so grave as respects the issue. If we contrast the characteristic hyperinotic state of the blood in inflammatory fever, displaying its bright colour, buffy coat, firm coagulum, and the adherence of the red corpuscles in rolls, with the septicæmic state of blood already described, showing its dark and dissolved state, loose coagulum, the red corpuscles adhering in clumps, and the increase of white corpuscles, we shall see well-marked grounds of distinction. This latter state of the blood is very similar to, if not identical with, that which belongs to typhous or adynamic fevers, and, indeed, in describing fatal cases of septicæmia after wounds the analogy of the symptoms is so great with these fevers that the word "typhous" is generally used in describing them. Hence the shortest discrimination of the indications for the use of *Pyrexin* or *Pyrogen* may be stated to be the typhous or typhoid character or quality of pyrexia, using these adjectives in their old-fashioned sense. For although the clinical discrimination of enteric fever from typhus is a great gain, it is unfortunate that the word "typhoid" should have been appropriated to the former, as it either introduces confusion into our nomenclature or deprives us of a hitherto well-understood expression of the character of pyrexia as distinct from the name of a specific disease. We shall find it convenient to go back to the terms of Cullen, viz. synocha, for inflammatory fever, the typhous or typhoid condition for the low adynamic or asthenic character or quality of fever, and synochus for the mixed kind, which is inflammatory at the beginning and typhous at the end. I do not know that the more accurate discrimination of the typhus, enteric, and relapsing fevers into distinct specific diseases gives any ground for denying the existence of the above distinctions of character in the pyrexial state in general, and, therefore, we should still keep up the words inflammatory, and typhous or typhoid, as expressive of different qualities or characters of fever, and not of distinct febrile diseases.

As *Aconite* is well known to be the most important of

the remedies for the synochal or inflammatory pyrexia, so the most summary indication for *Pyrogen* would be to term it the *Aconite* of the typhous or typhoid quality of pyrexia. This being a condition and not a distinct disease, it is to be looked for as occurring in a variety of diseases such as the typhus and enteric fevers themselves always, and more or less it may occur in intermittents, so-called bilious remittents, in certain varieties or stages of the exanthemata, especially scarlatina, measles, and smallpox, of dysentery, and of epidemic pneumonias, diphtheria, &c. From the gastro-enteric symptoms *Pyrogen* may possibly also apply to some stage of cholera, and to yellow fever. It is, of course, to be distinctly understood that this substance is only recommended at certain stages and phases of these diseases, and entirely as a remedy of a secondary or subordinate character, and not in any sense as a *specific* for the whole disease.

*Sepsin* or *Pyrogen*, it must be remembered, is only a chemical poison, like *Atropin* or serpent venom, whose action is definite and limited by the dose, and it is incapable of inducing an indefinitely reproducible disease in minimal dose, after the manner of the special poisons of the specific fevers; its sphere, therefore, is by no means commensurate with that of these diseases, and if ever true specifics for them should be discovered it is hardly probable that such would be merely chemical non-living agents. At present there is no question at all of such specifics. The only point is that we should be able to form an intelligible idea of the way in which a margin can be supposed to exist in individual cases, say of enteric fever, smallpox, or yellow fever, &c., in which a directly acting medicine can do good to the pyrexia without at the same time having any power to check, modify, or shorten the true specific disease. Observation, I think, shows that such a margin exists, for we are all familiar with the immense variety in the degree of severity, especially as regards the pyrexia existing between cases of the same specific fever in different individuals, while at the same time the cardinal symptoms are pronounced sufficiently to leave no doubt of the diagnosis,

and the completeness of the specific process is also shown by the protection against subsequent attacks being as complete after the slight cases as after the more severe. In scarlatina and smallpox both these circumstances are notorious, and the astonishing mildness of the pyrexia in some case of enteric fever, in which the local diseased process runs its full course, is well known.

When we take these facts in connection with the theory of Beale that not all—nay, not even the majority—of the new bioplasts, whose formation and continued multiplication constitutes the essence of fever and inflammation, are, in a specific contagious disease, themselves specific, and capable of conveying the disease, we can easily see that there may be in each specific fever a large margin of non-specific febrile action or protoplasmic change. It may be, and probably is, this which gives the severity and fatality to certain cases by its excessive amount rather than the greater intensity of the specific process, owing to increased susceptibilities of the patient towards the specific poison, although no doubt that is also a factor of importance in the variations of severity in different individuals. At all events, we easily see from the above considerations the reasonableness of the expectation that any remedy which could moderate and control the concomitant non-specific pyrexia in the specific fevers would thereby palpably diminish the average mortality, even though it could not cut short the specific disease itself. Whether *Pyrogen* be such a remedy remains to be seen; at present we have only to show that a place is open for a possible agent of this kind. Our expectations, also, must not be pitched too high, because, for innumerable reasons, as we all know, a considerable mortality must attend all the severe specific fevers, and the margin wherein positive curative treatment adds to the value of good negative treatment is not large. Besides, from the very character of the symptoms and stage of the disease for which this remedy is indicated, it must often be in the position of a forlorn hope. Therefore, it is only by the statistical comparison of a large number of cases that we can determine how far lives have been saved by it.

The known specific fevers do not by any means exhaust the possible sphere of a remedy for the "typhous" condition of pyrexia; for, although it is no longer the fashion to speak of the synochus of Cullen, yet, as far as my experience goes (and I doubt not other practitioners will agree with me), the list of species or varieties of continued fever in this country is by no means exhausted when we name the inflammatory, rheumatic, typhus, enteric and relapsing. On the contrary, we all meet with cases of fever which cannot be distinctly referred to local lesion, and cannot be fairly brought under any of the above names, and for want of a more definite appellation we have to speak of as catarrhal, gastric, or bilious fever; or describe in some such vague way. Many of these are synochal, and require *Aconite* at the outset, while in the later stages a more adynamic state sets in, supposed to require stimulants, thus corresponding to the synochus of Cullen. In the specific fevers also, there may occur more or less of this primary and secondary quality of the pyrexia requiring *Aconite* at the first stage and (should our anticipation prove correct) *Pyrogen* at the later stages. Doubtless Cullen, his contemporaries, and for long his successors, described and treated as synochus many cases of continued fever, which were, in reality, enteric, or even relapsing, before Henderson separated the latter, or Jenner the former, from the general mass of continued fevers; and, no doubt, we are all doing the same in respect to other species to be discriminated in future. But this is of less consequence as regards medicinal treatment as long as we are guided by indications for a particular quality of pyrexia, and not the concrete disease in which that may occur. If the discrimination of enteric fever as a species may be correctly held to explain away synochus in part, yet can we admit that the supervention of bacterial growth at the later stage will account for all the rest? Certainly, in that case, the sepsin of the Bacteria would produce a state of blood analogous to the "typhous" state, and if itself the cause would of course exclude our remedy. But although a certain growth of micrococci does take place in some cases, and is the cause of complications

(*e. g.* ulcerative endocarditis in smallpox), yet there is certainly no proof and, I think, very little probability, that such is general and sufficient to account for the phenomena, which in the meantime must, therefore, be referred to a quality of the disease.

In septicæmia, metastatic pyæmia, and puerperal fever, it is more difficult to see any possible opening for a remedy of this kind. As long as not only sepsin, but bacteria, micrococci, and their germs are being poured into the system from the focus of infection we can naturally expect nothing good from it; but after the focus is removed or neutralised by antiseptics it may become a question whether the artificially prepared *Pyrogen* from a different source may not be curative in the still remaining fever and blood disorder. Likewise, whether it may not be a preventive of traumatic pyæmia and septicæmia if given when the system is verging on that loss of vital resistance which allows the development of these diseases. The above objection applies more particularly to auto-infective puerperal septicæmia, or that form which is apparently spontaneous, *i. e.* not arising from inoculation of specific infective poison such as that of erysipelas, of scarlatina, or of another case of puerperal fever itself. But in the latter case if, at an early stage, this remedy can control the degree of pyrexia, and thus hinder the loss of vital resistance which allows the development of metastatic pyæmia and septicæmia, it may be of vital importance and sensibly diminish the average mortality of that, at present, almost hopeless disease. For, as elsewhere* said, I look upon the theory which attributes the specific infective poisons to partial bions or portions of diseased protoplasm thrown off by the patient (Beale), to be true rather than that of specific pathogenic bacterial parasites. Disease having thus begun in a subject who may be regarded as having a deep-seated wound, vital resistance is lowered and the ubiquitous putrefactive bacteria grow and multiply locally, pass into the system, and add the fatal complications of pyæmia and septicæmia.

The theory of the engraftment of bacterial septicæmia

* *The Germ Theories of Infectious Diseases.* London: Baillière.

and pyæmia as a subordinate phenomenon upon other diseases, without the inoculation of a necessarily specific kind of Bacteria may be shortly stated as follows. The viable germs of a variety of kinds of Bacteria and micrococci existing constantly in all ordinary air and water, and articles of food and drink, even in some after cooking, we are constantly receiving them into the alimentary canal, air passages, and any open wound. But just as constantly in the healthy state does the living matter consume them and prevent their development, such powers being summed up in the term vital resistance. Many states of disease, however, especially traumatic and other states of pyrexia and local stagnation of the circulation, so far lower vital resistance, that the accidental Bacteria germs may grow and multiply, and thus add their characteristic noxious effects to the former disease. Many of the products of bacterial putrefaction, especially those comprised under the term *Sepsin,* have a powerfully poisonous influence in lowering and paralysing vital resistance, and thus a small quantity of complete putrilage, containing both living Bacteria and septic products, is able to form a focus from which septic growths and products can spread and infect the whole system fatally. But if the same amount of Bacteria alone is carefully washed from adhering *Sepsin,* no evil follows, for the vital resistance at the spot destroys the Bacteria speedily. This was proved by Hiller, who injected into his own arm a whole Pravaz syringeful of fluid swarming with living but carefully-washed Bacteria, and no effect was produced but a transitory redness of the part. If, therefore, *Sepsin* should prove a remedy for any of the forms of pyrexia, especially the traumatic, which lower vital resistance, to that extent we may expect it to be a *preventive* of those forms of pyæmia, septicæmia, and so-called blood poisoning, which depend on the development of accidentally introduced germs of Bacteria and micrococci.

In chronic disease there may also be an opening for a substance like this, acting so powerfully on the blood. Here we may name leucocythæmia, and possibly pernicious anæmia, also the disposition to boils, whitlows, and abscesses.

It may be said that the analogy is not great between the action of *Pyrogen* and leucocythæmia; but this may be merely that we see usually an early stage of that disease, whereas the final stage may complete the resemblance. I had the opportunity of following to its close a case of leucocythæmia with enlarged spleen, in which the number of the white corpuscles almost equalled that of the red. For many months little alteration of the health was apparent, except muscular debility and liability to digestive derangements. The patient, had, however, bled over much when a tooth was extracted, and also was subject to occasional bleeding of the nose, and once had hæmatemesis. Then, after cold or a trifling indigestion, there came on vomiting and purging, prostration, fever, delirium, and death, in about a week,—the course of the disease resembling typhus without any diagnostic mark of that disease. A day or two before death there was large extravasation of blood under the skin of a large surface of the trunk, a portion of which, drawn off by the aspirator during life, showed a tarry colour and consistence, and the same large proportion of white corpuscles, but no Bacteria. There was also complete deafness for a week, and nearly complete blindness for the last three days, thus reminding us of the retinal hæmorrhage in septicæmia. After death the only appearance of importance was the enlargement of the spleen. In this case, *Phosphorus*, *Arsenic*, and a variety of medicines failed.

A case of leucocythæmia is reported by Dr. Gowers,* in which retinal hæmorrhage is described and figured. Epistaxis is also mentioned as occurring frequently, but the termination is not given. This disease would seem to be analogous to a long drawn out first stage of *Sepsin* poisoning, therefore, since other remedies fail I would be inclined to try the one under consideration.

Such is an *à priori* outline of the possible sphere of action therapeutically of this powerful pyrogenic agent. It is, however, only an outline, as the characteristic alterations of the blood especially are too meagre and general to enable us to fill up the picture and give exact indications.

* *Medical Ophthalmoscopy*, p. 312.

What the exact state of the blood which characterises this typhous state is, is not yet made out, and it would appear from the observations of Andral and Gavarret, and more recently of Baxter and Willcocks, that the blood-corpuscles are less affected in number and richness in hæmoglobin than might have been expected in many cases of scarlet fever, measles, typhus, and typhoid; while, on the other hand, the decrease of the red corpuscles both in number and richness is most marked and rapid in paludal miasmatic fevers. The indications for pyrexin here given are entirely *à priori*, as the foregoing was all written before a single therapeutic experiment was made. We must, therefore, expect that experience may correct or fill up, or contradict a large part of the above anticipations. In order to put the matter to the test, I prepared some of Panum's *Sepsin* in the following three different ways.

*Modes of preparation of Sepsin.*

1st. Half a pound of chopped lean beef was put into one pint of water from the tap and set to macerate on the sunny side of a wall in June, 1879. As the weather was unusually cold and cloudy no pellicle had formed in fourteen days, so it was left a week longer. The maceration fluid was then reddish, thick, and fetid; this was strained through muslin, then filtered. The filtration was slow and difficult. The filtered liquid was then evaporated to dryness in a water-bath at boiling heat. The dry residue formed a brownish caky mass, which was then rubbed up in a glass mortar with two ounces of rectified spirits of wine, and then allowed to digest two hours. This sprituous maceration was then boiled for five minutes, then filtered. The residue on the filter was then thoroughly dried in the warm chamber, and formed a hard brownish mass, weighing fifty-four grains. This was rubbed up with 540 minims of distilled water, allowed to stand an hour and a half, and then filtered. The clear amber-coloured liquid which passed through is the watery extract or solution of *Sepsin*. To this was added double the volume, *i.e.* 1080 minims, of *Glycerine*, and labelled "*Pyrexin*" $\phi$, forming the standard solution of *Sepsin*, of which one minim corresponds to the water extract of $\frac{1}{30}$th of a grain of dry *Sepsin*. The solu-

tion is amber-coloured, and remains perfectly clear throughout, and without any trace of mould fungi on the surface eight months after preparation. On testing by subcutaneous injection in white mice in quantities from one minim upwards, and with simultaneous control experiments with like quantities of pure *Glycerine* diluted with one third water, it was found that one, two, and three minims produced palpable effects, though not fatal, while four minims were fatal in some cases, and six minims uniformly so, the correspouding control experiments being innocuous.

2nd Mode. A similar maceration, after standing fourteen days in July, 1879, was strained through a linen cloth, measured twelve ounces, of a deep and clear solution. This was at once precipitated with twelve ounces of strong spirits of wine (90°), mixed thoroughly by stirring, and set aside to stand all night. The precipitate was buff-coloured, and very bulky, taking up nearly half of the glass beaker. The supernatant alcohol was decanted off and the precipitate drained upon a filter, then washed off into a beaker with boiling spirit, made up to twelve ounces, and boiled over the lamp for five minutes with constant stirring. Filtered and washed with boiling spirits. The precipitate was removed to a clock-glass, and kept *in vacuo* over strong sulphuric acid for thirty-six hours, during which time it shrivelled into a small compass, and became blackish. It weighed forty-two grains. Now treated with ten parts of cold water for an hour in a mortar, triturating constantly. Then filtered and washed twice over. The two filtrates and washings were then evaporated in a water-bath to dryness, and weighed 1·5 grain. This was triturated in an agate mortar with 150 minims of a mixture of one part of water and two parts of *Glycerine*. This was marked *Sepsin* or *Pyrexin*, 100 minims = 1 grain. The solution is not complete, and flocculent particles are visible. Of this three minims are fatal to mice, and it is thus, therefore, more virulent than the former preparation, but from the small quantity of dry precipitate got and the large quantity of *Alcohol* consumed in the process it is not one to be recommended.

3rd Mode. A similar maceration of the nineteenth day, in the open air of a cold September. The filtered maceration liquid (11·3 ounces) was mixed at once with two volumes of rectified spirits of wine and precipitated. The precipitate was of a dull

brown colour, and the solution containing it was allowed to stand six days, then filtered, drained, and washed with hot spirits of wine. The precipitate was detached from the filter, dried in a warm chamber at 150° for eighteen hours, then ground very fine, and weighed 3·14 grammes = $48\frac{3}{4}$ grains. This was macerated six hours over a water-bath with ten parts of water, then twenty parts of *Glycerine* added, and filtered under pressure. The fluid was very pale amber-coloured, and keeps perfectly like the mode No. 1. But seven drops are not uniformly fatal to mice. It is, therefore, weaker than the first mode, and more *Alcohol* is consumed. The first mode is preferable in yielding a product of sufficient strength and in tolerable quantity, and with moderate expense of *Alcohol*. But it has the drawback that the preliminary evaporation is attended with such a horrible smell.

As above said these preparations were tested on mice, which animal had been found by Dr. R. Koch to react very like the human subject with the septic and anthrax poisons. The symptoms observed were as follows:—The animal became dull and languid, ceased to eat; then appeared restlessness, the eyes dim and sunken, and bleeding from the anus; then a quiet stupor till death. More or less of these symptoms were produced by all the doses, from one dose upwards. Bleeding from the anus was perceived in all the fatal cases, but also in some that recovered.

The blood of the animals thus killed was then tested by subcutaneous injection into healthy mice, which in every instance were unaffected. It was, therefore, not infectious, and we have thus the security that we are dealing with a simple non-reproducible chemical poison, whose effects can be regulated and kept within perfectly safe bounds by simply limiting the dose.

As all doses below six minims were insufficient to kill a mouse, we may take it that from one to five minims would be quite safe for subcutaneous injection for man. How much smaller might be sufficient for the curative reaction can only be determined by experience. As this is an animal poison like snake venom, it may require to be used subcutaneously, as we do not know how far the stomach or the mucous membrane may not impair its activity, as they cer-

tainly do with snake poison. This also can only be determined by experiment, and it may turn out to be effective in the much more convenient way of administration by the mouth. As the action of *Sepsin* is speedily exhausted, it would probably be necessary to repeat the dose by subcutaneous injection at least twice a day in acute pyrexia; and from the nature of its possibly curative operation, we would not expect a rapid or palpable lowering of febrile heat soon after each dose, but only a gradual amelioration of the disease.

As *Sepsin* is of the nature, probably, of peptones, and extremely favourable to the growth of accidental Bacteria, whose germs exist in all ordinary water, it should, if given internally, not be prescribed in an aqueous mixture, but dispensed in pure *Glycerine* or in *Glycerine* with one third of distilled water, and the dose dropped into a spoonful of water at the time of administering.

Since the above was written, I have had some experience with *Pyrexin* as a remedy, both subcutaneously and internally used, but not sufficient for publication. So far, however, the results have been favourable and give good promise. The injection, even of that strong *Glycerine* preparation, excites no local disorder, nor any general septic disturbance in the above doses. The first decimal dilution has been given internally, in three-drop doses frequently repeated, to children with good effect.*

* Messrs. Thompson and Capper, chemists, 55, Bold Street, Liverpool, have undertaken to prepare *Pyrexin* according to formula No. 1, to ensure uniformity of strength and quality. They will furnish it in the form above described as *Pyrexin* $\phi$, and also in the first decimal dilution.

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